# UNITED STATES PATENT AND TRADEMARK OFFICE

## BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte DANIEL J. DRUCKER and JULIE LOVSHIN



Appeal No. 2004-2356
Application No. 09/833,740

HEARD: March 10, 2005

Before ELLIS, GRIMES, and GREEN, Administrative Patent Judges.

GREEN, Administrative Patent Judge.

## DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1-5 and 9-11.[1] Claims 1, 9, 10 and 11 are representative of the subject matter on appeal, and read as follows:

> 1. A recombinant DNA construct, comprising a promoter region of a GLP-2 receptor gene and linked for expression therewith, a heterologous gene of interest, wherein the promoter region comprises at least the last 1,000 nucleotides upstream of the transcription start site of (A) the murine nucleotide sequence of SEQ ID NO.1 or (B) a mammalian homolog of said nucleotide sequence.

[1] Claims 6-8 stand withdrawn from consideration as being drawn to a non-elected invention. See Appeal Brief, page 2.

9. A recombinant DNA construct according to claim 1, wherein said promoter region is a mammalian homolog which is a human homolog comprising at least residues -1 to -203 illustrated in Figure 7b (bases 1-201 of SEQ ID NO: 7).

10. A recombinant DNA construct according to claim 1, wherein the promoter region comprises from 1.5 kb to 10.6kb of the murine GLP-2 receptor promoter.

11. A recombinant DNA construct according to claim 10, wherein said promoter region comprises the nucleotide sequence of SEQ ID NO.1.

The examiner does not rely upon any prior art.

Claims 1-5 and 9-11 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention, i.e., lack of an adequate written description. In addition, the claims stand rejected under 35 U.S.C. § 112, second paragraph, for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention. After careful review of the record and consideration of the issues before us, we affirm the rejection under 35 U.S.C. § 112, first paragraph, but reverse the rejection under 35 U.S.C. § 112, second paragraph.

## BACKGROUND

Glucagon-like peptide 2, the specification notes, is "a 33 amino acid product of the preglucagon gene," and "has been described as a potent growth factor for gastrointestinal tissue, including the large bowel, upper GI, and

particularly, the small bowel, which acts by stimulating cellular proliferation and inhibition of cell death." Specification, page 2. The receptor for the GLP-2 peptide (GLP-2R) "is expressed in a highly tissue specific manner predominantly in gut endocrine cells and in the brain," although "little is known about either the expression or function of the GLP-2R in different regions of the [central nervous system]." Id. at 4.

According to the specification,

> [t]he present invention exploits the promoter region of the GLP-2 receptor gene. The GLP-2 receptor gene ("GLP-2R gene") is characterized as that region of genomic DNA that mediates production of a GLP-2 receptor having the structural and functional properties reported in the literature . . . .
>
> In other words, the GLP-2R receptor gene includes not only the coding region and the 5'-UTR . . . but also a 5' flanking region, described here, which functions as a tissue-specific promoter in vivo. More specifically, it has been discovered that the promoter region which drives expression of the endogenous GLP-2R gene coding region begins 5' to the first base of the 5'-UTR and extends upstream therefrom to include, minimally, the number of bases necessary to drive transcription at levels above detectable background. Thus, the promoter region comprises at least about 1,000 bases upstream of the transcription start site, suitably at least 1,200 bases upstream thereof, and desirably at least 1,400 bases 5' thereof. The maximum size of the promoter region can extend beyond 8,000 bases upstream of the transcription start site, and desirably incorporates those components, such as transcriptional factor binding sites and upstream activator sequences, through which expression of the endogenous GLP-2R gene normally is regulated.

Id. at 10.

## DISCUSSION

### Written Description

Claims 1-5 and 9-11 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention, i.e., lack of adequate written description.

We initially note that appellants argue that claims 1-5 stand or fall together, and claims 9, 10 and 11 each stand or fall alone. See Appeal Brief, page 7. As claims 1-5 stand or fall together, we focus our analysis of that group on claim 1.

The Court of Appeals for the Federal Circuit, our reviewing court, has addressed the issue of what constitutes an adequate written description for a claim drawn to a nucleic acid. In Enzo Biochem, Inc. v. Gen-Probe Inc, 323 F.3d 956, 63 USPQ2d 1609 (Fed. Cir. 2002), the court adopted a portion of the Guidelines proffered by the United States Patent and Trademark Office (USPTO). The court stated that:

> The written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of characteristics."

Enzo Biochem, 323 F.3d at 964, 63 USPQ2d at 1613 (citing Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, ¶ 1 "Written Description" Requirement, 66 Fed. Reg. 1099, 1106 (January 5, 2001)).

The court also addressed the issue of what constitutes an adequate written description of a claim to a broad genus of sequences. In The Regents of The University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997), the court determined that the disclosure of rat cDNA did not provide adequate written description support for claims drawn to mammalian and vertebrate DNA. Eli Lilly, 119 F.3d at 1567-68, 43 USPQ2d at 1405. The court stated:

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.

In Enzo-Biochem, the court refined the approach advanced by Eli Lilly, adopting an example offered in the USPTO guidelines having facts that contrasted with those of Eli Lilly, wherein the written description requirement would be met. Thus, an adequate written description may be present for a

genus of nucleic acids based on their hybridization properties, "if they hybridize under highly stringent conditions to known sequences because such conditions dictate that all species within the genus will be structurally similar." Enzo Biochem, 323 F.3d at 967, 63 USPQ2d at 1615.

According to the rejection, claims 1-5, and 9 "are broadly directed to a recombinant DNA construct comprising 'a promoter region of a GLP-2 receptor gene', (GLP-2R promoter), which comprises at least the last 1000 nucleotides upstream of the start site of transcription of either the murine nucleotide sequence of SEQ ID NO: 1 (isolated from mouse) or a mammalian homolog of the nucleotide sequence of SEQ ID NO: 1." Examiner's Answer, page 3.

With respect to disclosed structures, i.e., sequences, of GLP-2R promoters, the examiner notes that the specification "describes the promoter as comprising at least 1000 base pairs upstream of the transcription start site," and also requiring "'the number of bases necessary to drive transcription at levels above detectable background,'" as well as "'transcription factor binding sites and upstream activator sequences, through which expression from the endogenous GLP-2R gene normally is regulated.'" Id. at 3-4 (quoting paragraph 43 of the specification). The examiner goes on to note that all that is disclosed by the specification, however, is "a sequence of about 1.5 kb from upstream of the transcription start site (a SmaI-PstI fragment, nucleotides 182-1673 of SEQ ID NO: 1) of the mouse GLP-2R gene . . . ." Id. at 4. Moreover, according to the examiner, if additional DNA regulatory sequences are needed "'to correctly

specify transgene transcription in all cells and tissues expressing the endogenous GLP-2R receptor,' the specification does not describe these additional sequences." Id. at 6.

The examiner acknowledges that "[t]he specification discloses approximately 200 bases upstream of the transcription start site of the human GLP-2R gene," but that the human upstream sequence was not disclosed, and that "[n]o structural information for the promoter of a GLP-2R gene for any other species of organism is disclosed." Id. at 6-7. Thus, according to the examiner, only a single species of the broadly claimed genus of a "promoter region of a GLP-2R receptor gene" is disclosed by the specification. See id. at 6.

With respect to functional characteristics of the GLP-2R promoter, the examiner states that "[t]he only assay disclosed in the specification relating to promoter function is to operably link the putative promoter sequence to a reporter gene, e.g. *lacZ*, make a transgenic mouse containing the construct and then compare the expression of the reporter to the expression of the endogenous mouse GLP-2R receptor in various tissues." Id. at 4. When that assay was conducted, however, the examiner explains "that the 1.5 kb mouse sequence directed expression of the reporter in similar but not identical tissues as the endogenous GLP-2R gene." Id. (emphasis added). Moreover, given the results from using the mouse sequence in a transgenic mouse, the examiner explains that it is unclear from the disclosure how the function of GLP-2R promoters from organisms other than the mouse is to be assessed. See id. at 7.

We agree with the above analysis, and find that the specification does not adequately describe the genus of GLP-2R promoter regions encompassed by claim 1, and the rejection is affirmed.

Appellants argue that the written description requirement is met as the disclosure sets forth a correlation between function and structure. See Appeal Brief, page 12.

Appellants assert that the specification sets forth the partial structure for both the murine (SEQ ID NO:1) and the human (SEQ ID NO:7) GLP-2R promoter region. See id. According to appellants, the murine sequence contains at least 1.5kb of the GLP-2R promoter region, while the human homolog includes at least 202 nucleotides. See id. In addition, appellants contend that the specification sets forth another physical property of the promoter region—its location. See id. at 13. The promoter region, as set forth in the specification, is located in the 5'-flanking region upstream of the transcription start site of the GLP-2R gene. See id.

Appellants assert further that "[t]he specification also discloses a correlation between the physical property of the claimed promoter regions and their function. Specifically, the specification teaches the correlation between the nucleotide sequences as located in the 5'-flanking region upstream of the transcription start site of the GLP-2R gene and the tissue-specific promoter function of the claimed promoter regions." Id.

Appellants' arguments are not convincing. Specifically, as to structure, the specification only teaches two partial structures, i.e., nucleotide sequences, of GLP-2R promoter regions. As noted by the rejection, the specification teaches a sequence of about 1.5 kb from upstream of the transcription start site of the mouse GLP-2R gene, and also teaches approximately 200 bases upstream of the transcription start site of the human GLP-2R gene. The claim, however, encompasses any mammalian homolog of the murine nucleotide sequence.

With respect to function, the only function disclosed by the specification is an assay wherein the promoter is operably linked to a reporter gene, which is then used to make a transgenic mouse, wherein the expression of the reporter is compared to the expression of the endogenous mouse GLP-2R receptor in various tissues. The only promoter for which data from the assay is provided in the specification is the mouse promoter, and as also noted by the specification, the 1.5 kb mouse sequence directed expression of the reporter in similar but not identical tissues as the endogenous GLP-2R gene. Thus, although the promoter region is defined as being "at least the last 1,000 nucleotides upstream of the transcription start site," there is no description of how other mammalian promoters would be expected to perform in the assay. And given the fact that the 1.5 kb mouse sequence did not direct expression in the identical tissues as the endogenous promoter, the skilled artisan would not expect all mammalian promoters to give identical results in the assay. We thus find that there is no

disclosure of structure coupled with function that would allow one skilled in the art to visualize or recognize the identity of the members of the genus.

Moreover, the correlation between the nucleotide sequences as located in the 5'-flanking region upstream of the transcription start site of the GLP-2R gene and the tissue-specific promoter function of the claimed promoter regions is not the type of structure-function correlation envisioned by the Federal Circuit in Enzo Biochem. First, the position of the promoter being defined as the 5'-flanking region upstream of the transcription start site of the GLP-2R gene may be a physical characteristic of the promoter, but it in no way describes the structure, i.e., the sequence of the promoter region. Second, Enzo Biochem describes a hybridization assay wherein the conditions dictate that all species within the genus will be structurally similar. The functional assay described by the specification, i.e., operably linking the putative promoter sequence to a reporter gene, making a transgenic mouse containing the construct, and then comparing the expression of the reporter to the expression of the endogenous mouse GLP-2R receptor in various tissues does not dictate that all of the species within the genus will be structurally similar. In fact, functional variants possessing as little as 75% sequence homology are contemplated by the specification. See Specification, page 15.

With respect to claim 9, appellants argue that "[t]he subject matter of claim 9 is fully described in the specification because the specification sets forth the recited sequence and teaches that the invention includes promoter regions

comprising that sequence." Appeal Brief, page 18. Appellants argue further that "Lilly does not apply to claim 9 because claim 9 does not define the promoter region by function only." Id.

Appellants' arguments are not convincing, because as noted by the examiner and as acknowledged by appellants, the specification only provides a partial structure for the human homolog of the GLP-2R promoter region. The specification only provides about 20% of the sequence, thus without the approximately 80% of the nucleic acid sequence not disclosed, we cannot say that the promoter as claimed has been described. In re Wallach, 378 F.3d 1330, 1334, 71 USPQ2d 1939, 1942-43 (Fed. Cir. 2004). Moreover, as has been already discussed above, the specification does not provide a functional assay that can be correlated to structure. Therefore, until appellants obtain a complete nucleotide sequence, "they have no more than a wish to know the identity" of the claimed promoter region. Wallach, 378 F.3d at 1335, 71 USPQ2d at 1943. Thus, the written description rejection as to claim 9 is also affirmed.

With respect to claim 10, appellants argue that "[t]he specification expressly sets forth at least 1.5 kb of the nucleotide sequence of the murine GLP-2R promoter region in Figures 1 and SEQ ID No: 1." Appeal Brief, page 19. Moreover, appellants thus contend that "the specification provides a partial structure for the claimed promoter regions in Figures 1 and 7b and SEQ ID NO: 1, discloses another physical property of the claimed promoter regions by teaching the location of the promoter region within the known murine GLP-2R

gene, and discloses the correlation between the nucleotides at that location and their function as a tissue-specific promoter." Id. at 20.

Again, we do not find appellants' arguments to be convincing. Claim 10 is drawn to the DNA construct of claim 1, "wherein the promoter region comprises from 1.5 kb to 10.6 kb of the murine GLP-2R receptor promoter." As noted by the examiner, see Examiner's Answer, page 6, the specification does not describe, i.e., provide additional nucleotide sequences, for the murine promoter region, other than the 1.5 kb of the nucleotide sequence of the murine GLP-2R promoter region in Figures 1 and SEQ ID No: 1. The claim, however, encompasses up to 10.6 kb of the murine promoter region. As noted by the specification, that region may also include transcription factor binding sites, upstream activator sequences, and additional regulatory sequences "through which expression from the endogenous GLP-2R gene is normally regulated." Specification, page 10, see also Specification, page 47. As the specification does not provide sequences of those additional regulatory elements, it does not provide an adequate written description of the promoter region comprising from 1.5 kb to 10.6 kb of the murine GLP-2R receptor promoter. The rejection as to claim 10 is therefore affirmed.

With respect to claim 11, appellants are essentially the same as for claim 10. Specifically, appellants argue that the specification provides a partial structure in SEQ ID NO: 1, teaches another physical property by teaching the location, and "discloses a correlation between the physical and functional

properties by teaching that the nucleotide sequence at that location is responsible for the tissue-specific function." Appeal Brief, page 22.

The rejection as to claim 11 is affirmed for the same reasons as set forth as to the rejection of claim 10. As noted above, the claim is not limited to the 1.5 kb region disclosed by the specification in SEQ ID NO:1, but also includes additional regulatory sequences that are not described the specification.

Indefiniteness

Claims 1-5 and 9-11 stand rejected under 35 U.S.C. § 112, second paragraph, for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention.

We initially note that the examiner has not separated the analysis under 35 U.S.C. § 112, first paragraph, lack of adequate written description, and 35 U.S.C. § 112, second paragraph, indefiniteness. The following, however, appears to be the best statement as to why the examiner finds the claims to be indefinite.

> [The] specification and claims do not clearly set forth the metes and bounds of "promoter region of a GLP-2 receptor gene" because it [sic, they] does not indicate what level of similarity in structure and tissue expression between the putative promoter sequence and the endogenous promoter are required for the putative promoter to be considered a "promoter region of a GLP-2 receptor gene." It is unclear, especially from the teachings in para. 0156, whether the 1.5 kb mouse GLP-2R DNA fragment is a "promoter region of a GLP-2R receptor gene" since it did not "correctly specify transcription in all cells and tissues expressing the endogenous GLP-2R receptor." It is unclear how dissimilar a putative promoter sequence can be to an endogenous GLP-2R promoter in terms of both structure and function, and still be a "promoter region of a GLP-2R receptor gene" required by the

> claims. Consequently, the claims do not meet the requirements of § 112, 2nd para.

Examiner's Answer, page 5.

"The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification." Miles Laboratories, Inc. v. Shandon, Inc., 997 F.2d 870, 875, 27 USPQ2d 1123, 1126 (Fed. Cir. 1993). The examiner's concerns, however, appear to be more concerns under 35 U.S.C. § 112, first paragraph, written description, rather than § 112, second paragraph. Thus, although the subject matter may not be adequately described as discussed above, the skilled artisan would understand the bounds of the claimed subject matter, and the rejection is reversed.

## CONCLUSION

The rejection of claims 1-5 and 9-11 under 35 U.S.C. § 112, first paragraph, for lack of adequate written description is affirmed for claims 1-5 and 9, but reversed for claims 10 and 11. The rejection of claims 1-5 and 9-11 under 35 U.S.C. § 112, second paragraph, for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention, is reversed for all the claims.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED

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